

EXHIBIT 10

BMJ Open Interactions between physicians and the pharmaceutical industry generally and sales representatives specifically and their association with physicians' attitudes and prescribing habits: a systematic review

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ABSTRACT

Objectives The objective of this review is to explore interactions between physicians and the pharmaceutical industry including sales representatives and their impact on physicians' attitude and prescribing habits.

Data sources PubMed, Embase, Cochrane Library and Google scholar electronic databases were searched from 1992 to August 2016 using free-text words and medical subject headings relevant to the topic.

Study selection Studies included cross-sectional studies, cohort studies, randomised trials and survey designs. Studies with narrative reviews, case reports, opinion polls and letters to the editor were excluded from data synthesis.

Data extraction Two reviewers independently extracted the data. Data on study design, study year, country, participant characteristics, setting and number of participants were collected.

Data synthesis Pharmaceutical industry and pharmaceutical sales representative (PSR) interactions influence physicians' attitudes and their prescribing behaviour and increase the number of formulary addition requests for the company's drug.

Conclusion Physician-pharmaceutical industry and its sales representative's interactions and acceptance of gifts from the company's PSRs have been found to affect physicians' prescribing behaviour and are likely to contribute to irrational prescribing of the company's drug. Therefore, intervention in the form of policy implementation and education about the implications of these interactions is needed.

INTRODUCTION

The relationship between physicians and the pharmaceutical industry has evoked heated debate for many decades.¹ In 2012, the pharmaceutical industry spent \$89.5 billion on physician-pharmaceutical sales representative (PSR) interactions that accounted for 60% of the global sales and marketing spending.²⁻⁸ Previous reports have demonstrated that

Strengths and limitations of this study

- Large up-to-date systematic review of studies exploring the impact of pharmaceutical industry representative interactions on physicians.
- This systematic review used the recommendations outlined in the Cochrane Handbook for conducting systematic reviews and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the quality of the evidence by outcome.
- PubMed, Embase, Cochrane Library and Google Scholar electronic databases were searched from 1992, as well as grey literature.
- Most studies identified were observational and of varying methodological design.
- Some studies did not provide evidence for the significance of their findings.

PSRs may influence prescribing behaviour.⁹⁻¹⁶ However, the evidence determining whether pharmaceutical industry and PSRs interactions influence physicians is divided and contradictory. Studies have indicated that physicians may be unable to distinguish between promotional information and scientific evidence.^{17 18} Physicians, however, believe their colleagues are more susceptible to pharmaceutical industry marketing strategies than themselves.¹⁹⁻²² The majority of the physicians do not believe that they are affected by pharmaceutical industry and PSR interactions. Most medical and governmental institutions have installed guidelines and self-regulatory and legislative checks to regulate the relationship between physicians and the pharmaceutical industry and its representatives.^{5 15 16 23-26} However, while administrative proposals for deregulatory reforms



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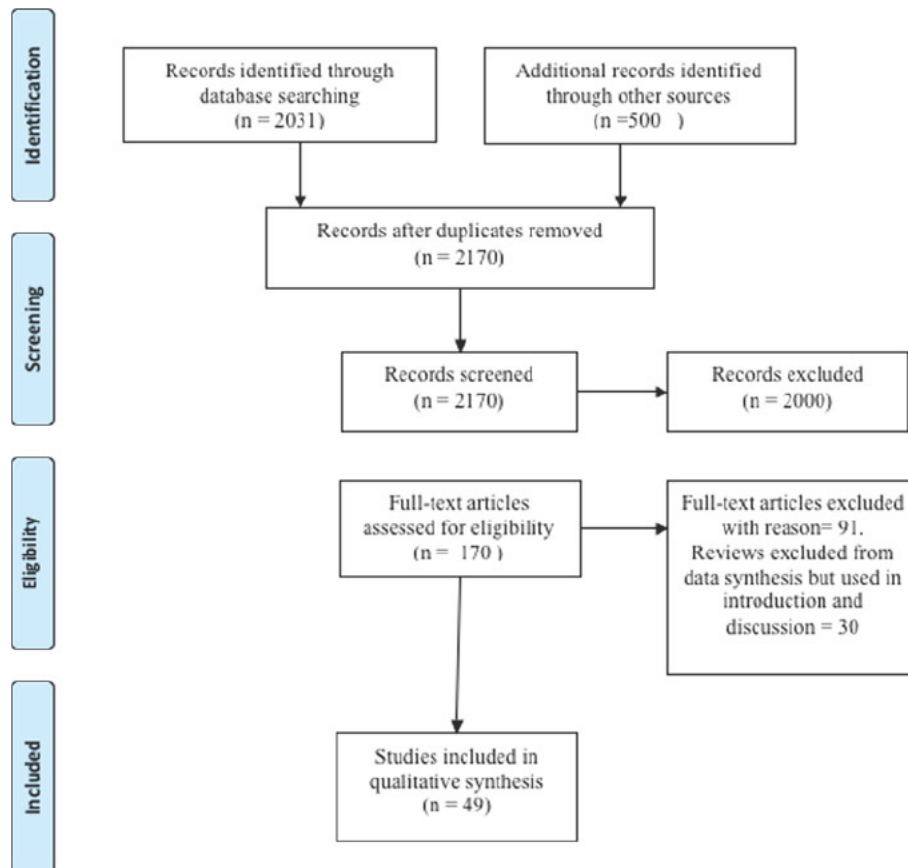


Figure 1 PRISMA flow diagram showing search strategy and included studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

that would remove some governmental authority over the industry are increasing, scientific evidence rigorously examining the extent of interactions between physicians and pharmaceutical industry and its PSRs is needed. This review evaluates critically and systemically the evidence on the impact of pharmaceutical industry and PSR interactions on physicians.

METHODOLOGY

Protocol

We followed a detailed methodology that we described in our review protocol, which is available on request to the corresponding author. Two independent reviewers assessed selected articles as per inclusion/exclusion criteria, shortlisted them for writing the review and cross-checked their decisions about inclusion/exclusion with each other. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (supplementary appendix 1).

Eligibility criteria

The eligibility criteria were:

- ▶ types of studies: observational study design, such as cross-sectional studies and cohort studies, but also (non-)randomised trials and survey designs comparing at least one facet that are mentioned below on the impact on behaviour and attitude;

- ▶ types of participants: physicians, pharmaceutical representatives and physicians in training/residents;
- ▶ types of exposure: any type of interaction between physicians and the pharmaceutical industry where there is direct interaction with the physician, such as meeting with drug representatives, participating in pharmaceutical-sponsored Continuing Medical Education (CME) events, receiving travel funding, free drug samples, industry-provided meals, gifts and presentations of industry-related information;
- ▶ types of outcome: knowledge, beliefs and/or attitudes of physicians regarding physician–industry interactions and (prescribing) behaviour of physicians;
- ▶ type of control: no interaction.
- ▶ Exclusion criteria were: qualitative, ecological, econometric studies, editorials, letters to the editor, studies on other health professionals (eg, nurses and medical students), small samples sizes, studies assessing indirect interactions and research funding.

We did not exclude studies based on risk of bias. We took risk of bias into account when grading the quality of evidence using GRADE approach.

Search strategy

The search strategy included PubMed, Embase, Cochrane Library and Google Scholar electronic databases (January 1992 to August 2016). Databases were not searched

before 1992, as these studies were already investigated in an earlier review.²⁷ The search combined terms for physicians and pharmaceutical and included both free-text words and medical subject heading relevant to the topic. We did not use a search filter. The online supplementary information file provides the full details for one database. Additional search strategies included a search of the grey literature (theses and dissertations). Also, we reviewed the references lists of included and relevant papers.²⁷⁻²⁹

Assessment of risk of bias in included studies

Two reviewers assessed in duplicate and independently the risk of bias in each eligible study. Disagreements were resolved by discussion or adjudication by a third reviewer. We used the recommendations outlined in the Cochrane Handbook to assess the risk of bias in randomised studies. We graded each potential source of bias and rated the studies as high, low or unclear risk of bias.

Data analysis and synthesis

The information extracted from the selected studies included type of study, study design, type of pharmaceutical industry and PSR interaction and type of outcome. We did not conduct a meta-analysis due to the heterogeneity of study design, types of interventions, outcomes assessed and outcome measures used. Instead, we summarised the data narratively. We assessed the quality of evidence by outcome using the GRADE methodology.³⁰

RESULTS

We independently screened the titles and abstracts of the 2170 identified records for potential eligibility. Out of 2170, the full text of 49 eligible citations that matched the inclusion criteria were retrieved and used for qualitative assessment during the writing of the review (figure 1, table 1).

Characteristics of included studies

The identified studies were published between 1992 and August 2016. Most of the studies included were cross-sectional studies.^{19-13 19 21 22 31-55} Only two studies were cohort studies,^{56 57} three were randomised trials⁵⁸⁻⁶⁰ and one study was a case-control study.⁶¹

Extent of interactions between physicians and the pharmaceutical industry

We found that PSR interactions are a regular feature in the daily lives of physicians across the world.^{9-11 13 42 50} Most of the attending physicians and residents have at least one interaction with industry representatives per month.^{10 21 22 36 42} The frequency of interactions or gifts offered and accepted varies with private versus public hospital setting and the position of the physicians in the medical hierarchy.^{10 13 31 38 42 43 50 58 62} Junior residents received twice as much free drug samples from PSR interactions than senior residents.¹⁰ PSR interactions were significantly higher at the beginning of residency.¹³ The majority of programme directors of internal

medicine residencies in the USA allowed PSRs to meet with residents during working hours and permitted PSR sponsorship of conferences.⁴⁰ Attending physicians and physician specialists had more PSR interactions and received higher numbers of medical samples and promotional material than residents.^{9 42} Participants working in private practice alone or in both sectors were more likely to receive gifts than physicians working in the public sector.^{38 42 50} Most common gifts received were medical samples,^{9 21 22 31 36 37 42 63} promotional material,^{9 34 42} invitations for dinners,⁹ invitations for CMEs,^{22 34} scientific journals³⁴ and free lunches.^{21 37}

Perspectives of physicians towards PSR interactions

We found that physicians have a positive attitude towards PSRs.^{1 13 19 20 22 31 32 40 49 58 64} Physicians perceived PSRs as important sources of education and funding,^{10 22 32 43 45 46} while some studies reporting sceptical attitudes about the contribution of PSRs towards teaching and education.^{21 36 39 40 49} Conference registration fees, informational luncheons, sponsorship of departmental journal clubs, anatomical models and free drug samples were considered as appropriate gifts.^{19 39 51 58} Most of the physicians considered pharmaceutical information provided by PSRs, industry-sponsored conferences and CME events as important instruments for enhancing their scientific knowledge.^{22 32 45 46} Compared with senior residents, significantly more junior residents felt that pharmaceutical representatives have a valuable teaching role.¹⁰

Most studies found that physicians do not believe that PSR interactions impact their prescribing behaviour,^{19-13 65 66} while other studies found that there was some extent of influence.^{21 22 34 36 37 39 43} In addition, physicians considered their colleagues more susceptible than themselves to PSR marketing strategies.^{1 20 21 37 43} There was a strong correlation between the amount of gifts and the belief that PSR interactions did not influence their prescribing behaviour.¹⁰

Gifts

We found that better scores on knowledge and attitudes were significantly associated with fewer interactions with representatives and their gifts.¹⁹ Conference registration fees, informational luncheons, sponsorship of departmental journal clubs, anatomical models and free drug samples were considered as appropriate gifts.^{19 37 47 52} Most of the physicians considered themselves immune to the influence of gifts.^{1 10 32 33 35 39 53 58} Most common gifts received were medical samples,^{9 21 22 31 36 37 42-44 47} promotional material,^{9 34 42 67} invitations for dinners⁹ and scientific journals.³⁴

Drug samples

Most of the physicians who accepted drug samples had a positive attitude towards the pharmaceutical representatives.^{9 21 22 31 36 37 42 43} Accepting samples lead to higher branded drug prescription rather than generic prescribing.^{22 47}



Table 1 Characteristics of included studies

Study	Authors	Country	Time frame	Participants, setting	Study design	Interaction	Outcomes
1	Steinman <i>et al</i> ¹	USA	Spring 1999	Surveys about attitudes and behaviours towards industry gifts in 105 residents at a university-based internal medicine residency programme	Cross-sectional	PSR Interactions, gifts	Most participants (61%) hold positive attitudes towards gifts from industry and PSR interactions and believe they do not influence their own prescribing, but only 16% believed other physicians were similarly unaffected ($p<0.0001$)
11	De Ferrari <i>et al</i> ⁶	Peru	March 2013	Questionnaire in 155 faculty and trainee physicians of five different clinical departments working in a public general hospital	Cross-sectional	PSR Interactions, medical samples, promotional material, dinners	Positive attitude towards representatives (88.5% of participants). Faculty physicians received a larger amount of medical samples and promotional material and were more prone to believe that gifts and lunches do not influence their prescribing behaviour (42.2% vs 23.6%; $p=0.036$)
12	Thomson <i>et al</i> ¹¹	New Zealand	1991	Questionnaire survey of 67 general practitioners	Cross-sectional	Interactions with PSR	Most general practitioners (67%) had a negative attitude towards PSR interaction
13	Kamal <i>et al</i> ²²	Egypt	July and August 2013	Interviews with 18 physicians	Cross-sectional	Interaction with PSR	Positive attitude towards PSR interaction
14	Hodges ¹⁰	Canada	October 1993–February 1994	Survey in 105 residents of psychiatry	Cross-sectional	Interaction with PSR, drug samples, lunches	Positive attitude towards PSR interaction (56.5% of participants). The more money and promotional items a participant had received, the more likely he or she was to believe that discussions with representatives did not affect prescribing ($p<0.05$)
15	Gibbons <i>et al</i> ²³	USA	Not reported	Survey of 392 physicians in two tertiary care medical centres	Cross-sectional	PSR Interactions, gifts, samples, travel, lunches	Positive attitude towards PSR interactions, gifts, samples and lunches
16	Spingarn <i>et al</i> ⁶	USA	February 1990	75 internal medicine physicians in university medical centre	Retrospective cohort	PSR interaction (teaching)	Attendees inappropriately prescribed PSR speakers drug compared with non-attendees ($p=0.029$)
17	Zaki ²⁵	Saudi Arabia	September–November 2013	Survey of 250 physicians	Randomised, cross-sectional survey	Conferences, drug samples	Favourable towards promotion
18	Orlowski <i>et al</i> 1994 ²⁷	USA	1987–1989	10 physicians that were invited for a symposium and tracking the pharmacy inventory usage reports for these drugs before and after the symposia	Cohort	Conference travel	Significant increase in the prescribing pattern of drugs occurred following the symposia ($p<0.001$)
19	Scheffer <i>et al</i> ²⁴	Brazil	2007–2009	Survey of 300 physicians prescribing antiretroviral drugs	Cross-sectional	Interaction with representative, drug samples, journals	Frequency of interaction; the majority of (64%) of the physicians had multiple forms of interactions with PSR

Continued

Table 1 Continued						
Study	Authors	Country	Time frame	Participants, setting	Study design	Interaction
20	Brett <i>et al</i> ⁶⁵	USA	Not reported	Questionnaire of 93 physicians in a medical school	Cross-sectional	Interaction with PSR
21	Gupta <i>et al</i> ⁶⁶	India	June–September 2014	Survey of 81 physicians in single hospital	Cross-sectional	Interaction with representative, drug samples, journals
22	Morgan <i>et al</i> ⁶⁷	USA	March 2003	Survey of 397 obstetrician-gynaecologists	Cross-sectional	Drug samples, promotional material, lunch
23	Alosalmi <i>et al</i> ⁶⁸	Saudi Arabia	2012	Survey of 659 physicians	Cross-sectional	Interaction with PSR
24	Chren and Landefeld ⁶¹	USA	1989–1990	40 case physicians and 80 control physicians	Case-control	PSR Interactions, honoraria, research
25	Randall <i>et al</i> ⁶⁹	USA	October 2001	Intervention group of physicians (n=18) that received education about PSR Interaction and control group (n=14)	Controlled trial	Interaction with PSR
26	Caudill <i>et al</i> ⁶⁸	USA	Not reported	Survey of 446 primary care physicians	Cross-sectional	Interaction with PSR
27	Andaleeb and Tallman ²⁰	USA	Not reported	223 physicians in northwestern Pennsylvania	Cross-sectional	Interaction with PSR
28	Reeder <i>et al</i> ⁶⁹	USA	1991–1992	87 residents of emergency medicine	Cross-sectional	Interaction with PSR, gifts
29	Lichstein <i>et al</i> ⁴⁰	USA	January–March 1990	272 directors of internal medicine residency programmes	Cross-sectional	Interaction with PSR
30	Brotzman <i>et al</i> ⁴¹	USA	Not reported	Directors of 386 family practice residency programme	Cross-sectional	Interaction with PSR
31	Alsaageer and Kowalski ⁴²	Libya	August–October 2010	Survey of 608 physicians in public and private practice settings	Cross-sectional	Interaction with PSR, drug samples, printed materials
Continued						



Table 1 Continued

Study	Authors	Country	Time frame	Participants, setting	Study design	Interaction	Outcomes
32	Lieb and Brandtonies, 2010 ²¹	Germany	2007	Survey of 208 physicians (neurology, cardiology and general medicine)	Cross-sectional	Interaction with PSR, drug samples, printed materials, lunches	Frequency and impact on attitudes
33	Lieb and Scheurich ²²	Germany	2010-2011	Survey of 160 physicians in private and public practices	Cross-sectional	Interaction with representative, drug samples, printed materials, CME	High expenditure prescribing; avoidance of industry-sponsored CME is associated with more rational prescribing habits
34	Lieb and Koch, ⁴³	Germany	May-July 2012	Survey of 1038 medical students at eight universities	Cross-sectional	Interaction with representative, drug samples, printed materials, lunches	Most participants have contact with the pharmaceutical company; 24.6% of the participants thought gifts would influence their future prescribing behaviour, while 45.1% thought gifts would influence their classmates' future prescribing behaviour (p<0.001)
35	Brown <i>et al</i> ⁴⁴	USA	2008 and 2013	251 directors of family medicine residency programmes	Cross-sectional	Interaction with PSR, gifts, lunches	Negative attitude towards PSR interactions
37	Rahman <i>et al</i> ⁴⁵	Bangladesh	December 2008-January 2009	Survey of 83 village physicians	Cross-sectional	Interaction with PSR	Impact on their prescribing
38	Lee and Begley, ¹²	USA	2008	Nationally representative survey of 4720 physicians	Cross-sectional	Gifts	Gifts were associated with lower perceived quality of patient care; an inverse relationship between the frequency of received gifts and the perceived quality of care was observed
39	Montastruc <i>et al</i> ¹³	France	August-October 2011	Survey among 631 medical residents	Cross-sectional	Interaction with representative	Most participants believed that PSR interaction had no impact on their prescribing; participants who had a more positive opinion were more frequently exposed to PSR (p<0.001)
40	Klemenc-Ketis and Kersnik ⁴⁶	Slovenia	October 2011	895 family physicians at the primary level of care	Cross-sectional	Interaction with PSR	Positive effect on knowledge; participants value PSRs' selling and communication skills and trustworthiness highly
41	Hurley <i>et al</i> ⁴⁷	USA	2010	3500 dermatologists	Cross-sectional	Free drug samples	Impact on their prescribing: the provision of samples with a prescription by dermatologists has been increasing over time, and this increase is correlated (r=0.92) with the use of the branded generic drugs promoted by these sample
42	Makowska ⁴⁸	Poland	November-December 2008	Survey of 382 physicians	Cross-sectional	Gifts	Positive attitude towards PSR interactions
43	Siddiqui <i>et al</i> ⁴⁹	Pakistan	Not reported	Questionnaires of 352 medical students	Cross-sectional	Interaction with representative	Positive attitude towards PSR interaction

Continued

Table 1 Continued							
Study	Authors	Country	Time frame	Participants, setting	Study design	Interaction	Outcomes
55	Workneh <i>et al</i> ⁶⁰	Ethiopia	February–March 2015	Survey of 90 physicians from public and private health facilities	Cross-sectional	Interaction with representative, gifts	Positive attitude towards industry, impact on prescribing behaviour; nearly half of the physicians reported that their prescribing decisions were influenced by PSR
57	Khan <i>et al</i> ⁶¹	Pakistan	Not reported	Questionnaires in 472 physicians	Cross-sectional	Interaction with representative, gifts	Positive attitude towards PSR interaction
58	Saito <i>et al</i> ⁶⁷	Japan	January–March 2008	1417 physicians working in internal medicine, general surgery, orthopaedic surgery, paediatrics, obstetrics-gynaecology, psychiatry and ophthalmology	National survey	Interaction with industry, receipt of gifts, funds, CME, samples	Positive attitude towards PSR and gifts, value information from PSR, interactions higher with physicians who prefer to prescribe brand names
59	Ziegler ¹⁸	USA	1993	27 physicians working in public and private hospitals	Survey	Accuracy of information provided by PSRs about drugs	Incorrect information often provided by speakers goes unnoticed by physicians
60	Lurie <i>et al</i> ⁶⁸	USA	Not reported	240 internal medicine faculty physicians in academic medical centres	Survey	Effect of interaction with PSR, free meals, honoraria and research support	Impact on prescribing behaviour and formulary change requests
62	DeJong <i>et al</i> ⁶²	USA	August–September 2013	279 669 physicians who wrote Medicare prescriptions in any of four drug classes: statins, cardioselective β -blockers, ACE inhibitors and angiotensin-receptor blockers, and selective serotonin and serotonin-norepinephrine reuptake inhibitors	Cross-sectional	Industry-sponsored meals	Receipt of industry-sponsored meals was associated with an increased rate of brand name prescription.
63	Yeh <i>et al</i> ⁶³	USA	2011	All licensed Massachusetts physicians who wrote prescriptions for statins paid for under the Medicare drug benefit in 2011 (n=2444)	Cross-sectional	Effect of industry payment on prescription of branded drugs for cholesterol control	Payment for meals and educational programmes increased prescription of brand name statins.
65	Bowman and Pearle <i>et al</i> ⁶⁹	USA	Not reported	121 physician attendees	Self-report survey	Effect of CME on prescribing behaviour	Sponsoring company's drugs were favoured during prescription
66	Fischer <i>et al</i> ⁶⁵	USA	November 2006–March 2007	Multidisciplinary focus groups with 61 physicians	Survey	Effect of industry marketing strategies on prescription and cognitive dissonance of physicians	Most participants reported no PSR impact on their prescribing, value to have ability to evaluate information of PSRs
67	Chimonas <i>et al</i> ⁶⁶	USA	June 2004	Six focus groups in 32 academic and community physicians	Survey	PSR interactions	Positive attitude towards PSR interaction
72	Yeh <i>et al</i> ⁶⁴	USA	Not reported	1610 US medical students	Cross-sectional	Interaction with representative, gifts, lunches	Policies separating students from representatives reduced number of interactions
73	Larkin <i>et al</i> ⁷³	USA	January 2006–June 2009	Paediatricians, child and adolescent psychiatrists in five medical centres	Survey	Interaction with PSR	Antidetailing policies reduced the prescription of off-label antidepressants and antipsychotics for children

Continued

Table 1 Continued

Study	Authors	Country	Time frame	Participants, setting	Study design	Interaction	Outcomes
74	Esmally <i>et al</i> ⁶⁰	Iran	Not reported	112 general physicians were randomised in two groups: (1) outcome-based educational intervention for rational prescribing and (2) concurrent CME programme in the field of rational prescribing	Randomised trial	Effect of outcome and rational prescribing	Rational prescribing improved in some of the important outcome-based indicators. No difference between two arms of the study
76	Parikh <i>et al</i> ⁶⁵	USA	2014	Descriptive, cross-sectional analysis of Open Payments data and 9 638 825 payments to physicians and paediatricians from 1 January to 31 December 2014	Cross-sectional	Comparison of PSR interactions between paediatricians and other specialists; among subspecialties of paediatricians.	Paediatricians get fewer gifts from PSR than internists. There is variation among subspecialties for extent of interaction.
78	Chressanthi <i>et al</i> ⁷⁴	USA	Not reported	Clinical decisions of 72 114 physicians were statistically analysed using prescription data	Survey	Effect of restricting PSRs on clinical practice and knowledge	Restricting PSRs affected information flow about drugs, both negative and positive.

We excluded 2000 records as they were not relevant (n=1641), not original research (n=269), about medical students (n=4) and non-medical (eg, ecological and econometric; n=86). PSRs, pharmaceutical sales representatives.

Pharmaceutical representative speakers

Sponsored lectures/symposia of pharmaceutical companies influenced behaviour of the attendees leading to the attendees prescribing more drugs from the sponsoring companies without sufficient evidence supporting superiority of those drugs.^{56 57} The majority of attending physicians failed to identify inaccurate information about the company drug.¹⁸

Honoraria and research funding

Physicians who received money to attend pharmaceutical symposia or to perform research requested formulary addition of the company's drug more often than other physicians. This association was independent of many confounding factors⁶¹ (table 2). Brief encounters with PSRs and receipt of honoraria or research support were predictors of faculty requested change in hospital formulary.⁶⁸

Conference travel

Pharmaceutical company-sponsored conference travels to touristic locations have quantifiable impact on the prescribing rational of attendees. A significant increase (three times) in the prescribing rate of two company drugs was observed after the physicians attended a company-sponsored symposium with all their expenses covered. Despite this significant difference in the prescribing patterns, physicians insisted there was no impact on their prescribing behaviour.⁵⁷

Industry-paid lunches

Most physicians received invitations for dinners⁹ and free lunches.^{10 21 35 43} Clerks, interns and junior residents attended more company-sponsored lunches than senior residents.¹⁰ Pharmaceutical companies also sponsored departmental lunches during journal clubs.³⁹ There was no significant association between attending industry-paid lunches³⁷ and dinners⁹ and formulary request for that company's drug (table 2).

CME sponsorship

Physicians who attended company-sponsored CME events had more positive attitudes towards and inclination to prescribe the branded drugs.^{28 34 43 67 69–71} We found that physicians who refused CME sponsorship were seen to prescribe higher proportion of generics and lower expenditure medicines when compared with physicians who attended CMEs.²²

DISCUSSION

We report that there is widespread interaction between the pharmaceutical industry and physicians.^{9–11 13 42 50} Interactions are in the form of personal communications, free gifts such as drug samples, sponsored meals, sponsored conference travel, funding for research and CMEs and honoraria.^{9 21 22 31 36 42} The frequency of these interactions is comparable between residents and physicians.^{10 21 22 36 42} However, the amount and type of gifts vary with the position

Table 2 Impact of physician-pharmaceutical industry interaction on physician

#	Attitudes	Prescribing behaviour	Knowledge	Formulary requests	Quality of evidence (GRADE)
Gifts	Receiving higher number of gifts associated with belief that PSR (pharmaceutical representative) have no impact on their prescribing behaviour ^{1,14,39}	-	-	-	Moderate
Drug samples	Positive attitude towards the drug industry and the representatives ^{1,11,21,34}	Higher prescription of the company drug ^{21,41}	-	-	High
Pharmaceutical representative speakers	-	Irrational prescribing ^{16,18,34}	Inability to identify false claims ¹⁶	Increased prescription of sponsor's drug ²⁴	High
Honoraria and research funding	Positive attitude towards sponsor's drug ⁶⁰	-	-	Increased prescription of sponsor's drug ²⁴	Low
Conference travel	-	Significant increase in prescribing of sponsor drug ¹⁸	-	Increased prescription of sponsor's drug ²⁴	Low
Industry-paid lunches	Positive attitude towards sponsor's drug ^{14,34}	Significant increase in prescribing of sponsor drug ²²	-	Increased formulary request for company drug ^{1,21}	High
CME sponsorship	Positive attitude towards sponsor's drug ^{24,65}	Avoidance of industry-sponsored CME associated with more rational prescribing habits ³³	-	-	Moderate
Interaction with PSR	Positive attitude towards PSR drugs ^{1,11,14,58}	Higher prescription of the company drug ²⁴	Positive correlation between the physicians' prescribing cost and the information provided by the drug representative during the interaction ²⁸	Increased prescription of sponsor's drug ²⁴	High

However, there was a significant association between attending industry-paid lunches and increased prescription of branded drugs.^{52,53,72}

of the physician in medical hierarchy, specialisation and location of practice.^{10 13 31 38 42 43 50 58 62} In general, trainees (residents and interns) are treated with more drug samples, stationery items and free meals than senior physicians.^{10 13} Senior physicians usually avail of sponsored conferences/trips, research funding, honoraria and CME events. The extent of these interactions varies with academic versus non-academic institutions: non-academic hospitals record more interactions than others.^{31 38 42 50 55} The majority of the physicians do not believe that they are affected by PSR interactions.^{1 10 32 33 35 37 43 59} However, a sizeable percentage in various surveys responded in the affirmative when asked whether they thought that their peers are vulnerable.^{120 21 37 43}

Policies and educational intervention

The relationship of physicians with patients is of a fiduciary nature. Hence, activities that might affect that relationship by altering physicians' clinical behaviour are not acceptable. Physician-pharmaceutical industry and PSR interactions may put the trust of patients in physicians at risk. Interaction with pharmaceutical industry and PSRs begins early in the physicians' career. Trainees are exposed to pharmaceutical industry marketing and promotional techniques from the initial years of their medical education, which impact their prescribing behaviour in future. Overall, trainees, that is, residents and interns, are more vulnerable to pharmaceutical industry and PSR interactions than senior physicians.^{11 41 62} Physicians are susceptible to pharmaceutical industry and PSR interactions, which influences their clinical decision making leading to greater prescriptions of branded drugs over low-cost generic medicines and increasing health-care costs.^{22 47 52 53 72} Therefore, there is need to institute and implement stringent policies curtailing physician-pharmaceutical industry and PSR relationships, as well as educational programmes to increase awareness. Previous reports have indicated that implementing policies and conducting educational programmes are effective in increasing awareness of physician's attitudes towards pharmaceutical industry and PSR interactions.^{54 59 60 73–83}

Strengths and limitations of the study

A major strength of this study is that it is a large, up-to-date systematic review of studies exploring the effects of physician and pharmaceutical industry representative interactions and residents in different settings (eg, academic and primary care). Another strength of this study is the use of Cochrane and GRADE methodologies for conducting a review and assessing the quality of the studies. Moreover, we performed an extensive search in three databases and the grey literature. Some of the limitations of this review are related to the included studies, as some did not provide evidence for the significance of their findings or had varying study designs and outcomes, which made it impossible to conduct a meta-analysis. Also, the included studies were subject to risk of bias related to the lack of validity of outcome measurement and inadequate handling of significant potential confounders.

Future implications

Pharmaceutical industry and PSR interactions compromise the objectivity of the physicians. Educating physicians and increasing regulation of pharmaceutical industry and PSR interactions may lower the likelihood of prescribing new non-superior industry drugs and irrational prescription behaviour. Further studies are required to evaluate the impact of pharmaceutical industry and PSR interactions on physicians over time and the benefits of various intervention-based education programmes on the clinical and ethical behaviour of the physicians.

Contributors All authors have contributed equally and have substantial contributions to the conception or design of the work: FF for the acquisition, analysis and interpretation of data for the work and drafting the work, EU and WF for revising it critically for important intellectual content and all authors contributed to final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Any data relevant to a published article will be made available alongside the article when published.

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REFERENCES

- Steinman MA, Shlipak MG, McPhee SJ. Of principles and pens: attitudes and practices of medicine housestaff toward pharmaceutical industry promotions. *Am J Med* 2001;110:551–7.
- Wazana A. Physicians and the Pharmaceutical Industry. *JAMA* 2000;283:373.
- Wolfe SM. Why do american drug companies spend more than \$12 billion a year pushing drugs? Is it education or promotion? *J Gen Intern Med* 1996;11:637–9.
- Wall LL, Brown D. The high cost of free lunch. *Obstet Gynecol* 2007;110:169–73.
- Chressanthi GA, Sfeka A, Khedkar P, et al. Determinants of pharmaceutical sales representative access limits to physicians. *J Med Market* 2014;14:220–43.
- International, K. Rising costs of litigation in pharmaceutical industry. Issues Monitor-Pharmaceuticals 2011;9:1–3.
- MedAdNews. Table insert on the top 50 pharma companies. Data provided by Cegedim Strategic Data 2010.
- Mack J. Pharma promotional spending in 2013. Pharma marketing news. 2014;13.
- De Ferrari A, Gentile C, Davalos L, et al. Attitudes and relationship between physicians and the pharmaceutical industry in a public general hospital in Lima, Peru. *PLoS One* 2014;9:e100114.
- Hodges B. Interactions with the pharmaceutical industry: experiences and attitudes of psychiatry residents, interns and clerks. CMAJ: Canadian Medical Association Journal, 1995;153:553.
- Riese F, Guloksuz S, Roventa C, et al. Pharmaceutical industry interactions of psychiatric trainees from 20 European countries. *Eur Psychiatry* 2015;30:284–90.
- Lee D, Begley CE. Physician report of industry gifts and quality of care. *Health Care Manage Rev* 2016;41:275–83.
- Montastruc F, Moulis G, Palmaro A, et al. Interactions between medical residents and drug companies: a national survey after the Mediator® affair. *PLoS One* 2014;9:e104828.
- Fugh-Berman A, Ahari S. Following the script: how drug reps make friends and influence doctors. *PLoS Med* 2007;4:e150.

15. Kesselheim AS, Mello MM, Studdert DM. Strategies and practices in off-label marketing of pharmaceuticals: a retrospective analysis of whistleblower complaints. *PLoS Med* 2011;8:e1000431.
16. Mulinari S. Unhealthy marketing of pharmaceutical products: An international public health concern. *J Public Health Policy* 2016;37:149–59.
17. Othman N, Vitry AI, Roughead EE, et al. Medicines information provided by pharmaceutical representatives: a comparative study in Australia and Malaysia. *BMC Public Health* 2010;10:743.
18. Ziegler MG. The Accuracy of Drug Information From Pharmaceutical Sales Representatives. *JAMA: The Journal of the American Medical Association*, 1995;273:1296.
19. Alosaimi FD AKA, Qadi M, Albahhal A, et al. Physicians' attitudes towards interaction with the pharmaceutical industry/Attitudes des médecins par rapport à l'interaction avec l'industrie pharmaceutique. *East Mediterr Health J* 2014;20:812.
20. Andaleeb SS, Tallman RF. Physician attitudes toward pharmaceutical sales representatives. *Health Care Manage Rev* 1995;20:68–76.
21. Lieb K, Brandtónies S. A survey of german physicians in private practice about contacts with pharmaceutical sales representatives. *Dtsch Arztebl Int* 2010;107:392–8.
22. Lieb K, Scheurich A. Contact between doctors and the pharmaceutical industry, their perceptions, and the effects on prescribing habits. *PLoS One* 2014;9:e110130.
23. Francer J, Izquierdo JZ, Music T, et al. Ethical pharmaceutical promotion and communications worldwide: codes and regulations. *Philos Ethics Humanit Med*, 2014;9:7.
24. Canada., C.o.f.p.o.C.R.c.o.p.a.s.o. Guide tot enhancing referrals and consultations between physicians. College of Family Physicians of Canada 2009.
25. Grande D. Limiting the influence of pharmaceutical industry gifts on physicians: self-regulation or government intervention? *J Gen Intern Med* 2010;25:79–83.
26. Brennan TA, Rothman DJ, Blank L, et al. Health Industry Practices That Create Conflicts of Interest. *JAMA* 2006;295:429.
27. Spurling GK, Mansfield PR, Montgomery BD, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review. *PLoS Med* 2010;7:e1000352.
28. Lexchin J. *Interactions between physicians and the pharmaceutical industry: what does the literature say?* CMAJ: Canadian Medical Association Journal, 1993;147:1407–7.
29. Wazana A, Granich A, Primeau F, et al. Using the literature in developing McGill's guidelines for interactions between residents and the pharmaceutical industry. *Acad Med* 2004;79:1033–40.
30. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
31. Thomson AN, Craig BJ, Barham PM. Attitudes of general practitioners in New Zealand to pharmaceutical representatives. *Br J Gen Pract* 1994;44:220–3.
32. Kamal S, Holmberg C, Russell J, et al. Perceptions and Attitudes of Egyptian Health Professionals and Policy-Makers towards Pharmaceutical Sales Representatives and Other Promotional Activities. *PLoS One* 2015;10:e0140457.
33. Gibbons RV, Landry FJ, Blouch DL, et al. A comparison of physicians' and patients' attitudes toward pharmaceutical industry gifts. *J Gen Intern Med* 1998;13:151–4.
34. Scheffer MC. Interaction between pharmaceutical companies and physicians who prescribe antiretroviral drugs for treating AIDS. *Sao Paulo Med J* 2014;132:55–60.
35. Brett AS, Burr W, Moloo J. Are Gifts From Pharmaceutical Companies Ethically Problematic? *Arch Intern Med* 2003;163:2213.
36. Gupta SK, Nayak RP, Sivaranjani R. A study on the interactions of doctors with medical representatives of pharmaceutical companies in a Tertiary Care Teaching Hospital of South India. *J Pharm Bioallied Sci* 2016;8:47.
37. Morgan MA, Dana J, Loewenstein G, et al. Interactions of doctors with the pharmaceutical industry. *J Med Ethics* 2006;32:559–63.
38. Caudill TS, Johnson MS, Rich EC, et al. Physicians, pharmaceutical sales representatives, and the cost of prescribing. *Arch Fam Med* 1996;5:201–6.
39. Reeder M, Dougherty J, White LJ. Pharmaceutical representatives and emergency medicine residents: a national survey. *Ann Emerg Med* 1993;22:1593–6.
40. Lichstein PR, Turner RC, O'Brien K. Impact of pharmaceutical company representatives on internal medicine residency programs. A survey of residency program directors. *Arch Intern Med* 1992;152:1009–13.
41. Brotzman GL, Mark DH. Policies regulating the activities of pharmaceutical representatives in residency programs. *J Fam Pract* 1992;34:54–8.
42. Alssageer MA, Kowalski SR. A survey of pharmaceutical company representative interactions with doctors in Libya. *Libyan J Med* 2012;7:18556.
43. Lieb K, Koch C. Medical students' attitudes to and contact with the pharmaceutical industry: a survey at eight German university hospitals. *Dtsch Arztebl Int* 2013;110:584–90.
44. Brown SR, Evans DV, Fugh-Berman A. Pharmaceutical industry interactions in family medicine residencies decreased between 2008 and 2013: a CERA study. *Fam Med* 2015;47:279–82.
45. Rahman MH, Agarwal S, Tuddenham S, et al. What do they do? Interactions between village doctors and medical representatives in Chakaria, Bangladesh. *Int Health* 2015;7:266–71.
46. Klemenc-Ketis Z, Kersnik J. Which pharmaceutical sales representatives' features do slovenian family physicians value? *Acta Inform Med* 2013;21:257.
47. Hurley MP, Stafford RS, Lane AT. Characterizing the relationship between free drug samples and prescription patterns for acne vulgaris and rosacea. *JAMA Dermatol* 2014;150:487.
48. Makowska M. Interactions between doctors and pharmaceutical sales representatives in a former communist country. The ethical issues. *Camb Q Healthc Ethics* 2014;23:349–55.
49. Siddiqui UT, Shakoor A, Kiani S, et al. Attitudes of medical students towards incentives offered by pharmaceutical companies – perspective from a developing nation – a cross-sectional study. *BMC Med Ethics* 2014;15:36.
50. Workneh BD, Gebrehiwot MG, Bayo TA, et al. Influence of Medical Representatives on Prescribing Practices in Mekelle, Northern Ethiopia. *PLoS One* 2016;11:e0156795.
51. Khan N, Abbas Naqvi A, Ahmad R, et al. Perceptions and Attitudes of Medical Sales Representatives (MSRs) and Prescribers Regarding Pharmaceutical Sales Promotion and Prescribing Practices in Pakistan. *J Young Pharm* 2016;8:244–50.
52. DeJong C, Aguilar T, Tseng CW, et al. Pharmaceutical Industry-Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries. *JAMA Intern Med* 2016;176:1114.
53. Yeh JS, Franklin JM, Avorn J, et al. Association of Industry Payments to Physicians With the Prescribing of Brand-name Statins in Massachusetts. *JAMA Intern Med* 2016;176:763.
54. Yeh JS, Austad KE, Franklin JM, et al. Association of medical students' reports of interactions with the pharmaceutical and medical device industries and medical school policies and characteristics: a cross-sectional study. *PLoS Med* 2014;11:e1001743.
55. Parikh K, Fleischman W, Agrawal S. Industry relationships with pediatricians: Findings from the open payments sunshine act. *Pediatrics* 2016;137:e20154440.
56. Spingarn RW, Berlin JA, Strom BL. When pharmaceutical manufacturers' employees present grand rounds. what do residents remember? *Acad Med* 1996;71:86–8.
57. Orlowski JP, Wateska L. The effects of pharmaceutical firm enticements on physician prescribing patterns. There's no such thing as a free lunch. *Chest* 1992;102:270–3.
58. Zaki NM. Pharmacists' and physicians' perception and exposure to drug promotion: A Saudi study. *Saudi Pharm J* 2014;22:528–36.
59. Randall ML, Rosenbaum JR, Rohrbaugh RM, et al. Attitudes and behaviors of psychiatry residents toward pharmaceutical representatives before and after an educational intervention. *Acad Psychiatry* 2005;29:33–9.
60. Esmaily HM, Silver I, Shiva S, et al. Can rational prescribing be improved by an outcome-based educational approach? A randomized trial completed in Iran. *J Contin Educ Health Prof* 2010;30:11–18.
61. Chren MM, Landefeld CS. Physicians' behavior and their interactions with drug companies. A controlled study of physicians who requested additions to a hospital drug formulary. *JAMA* 1994;271:684.
62. Zipkin DA, Steinman MA. Interactions between pharmaceutical representatives and doctors in training. A thematic review. *J Gen Intern Med* 2005;20:777–86.
63. McMurray RJ. *Gifts to Physicians From Industry*. JAMA: The Journal of the American Medical Association, 1991;265:501.
64. Lotfi T, Morsi RZ, Rajabbik MH, et al. Knowledge, beliefs and attitudes of physicians in low and middle-income countries regarding interacting with pharmaceutical companies: a systematic review. *BMC Health Serv Res* 2016;16:57.
65. Fischer MA, Keough ME, Baril JL, et al. Prescribers and pharmaceutical representatives: why are we still meeting? *J Gen Intern Med* 2009;24:795–801.

66. Chimonas S, Brennan TA, Rothman DJ. Physicians and drug representatives: exploring the dynamics of the relationship. *J Gen Intern Med* 2007;22:184–90.
67. Saito S, Mukohara K, Bito S. Japanese practicing physicians' relationships with pharmaceutical representatives: a national survey. *PLoS One* 2010;5:e12193.
68. Lurie N, Rich EC, Simpson DE, et al. Pharmaceutical representatives in academic medical centers. *J Gen Intern Med* 1990;5:240–3.
69. Bowman MA, Pearle DL. Changes in drug prescribing patterns related to commercial company funding of continuing medical education. *J Contin Educ Health Prof* 1988;8:13–20.
70. Grundy Q, Bero L, Malone R. Interactions between non-physician clinicians and industry: a systematic review. *PLoS Med* 2013;10:e1001561;10:e1001561.
71. Dixon D, Takhar J, Macnab J, et al. Controlling quality in CME/CPD by measuring and illuminating bias. *J Contin Educ Health Prof* 2011;31:109–16.
72. Steinbrook R. Industry Payments to Physicians and Prescribing of Brand-name Drugs. *JAMA Intern Med* 2016;176:1123.
73. Larkin I, Ang D, Avorn J, et al. Restrictions on pharmaceutical detailing reduced off-label prescribing of antidepressants and antipsychotics in children. *Health Aff* 2014;33:1014–23.
74. Chressanthi GA, Khedkar P, Jain N, et al. Can access limits on sales representatives to physicians affect clinical prescription decisions? A study of recent events with diabetes and lipid drugs. *J Clin Hypertens* 2012;14:435–46.
75. Silverman E. Everything you need to know about the Sunshine Act. *BMJ* 2013;347:f4704.
76. Shalowitz DI, Spillman MA, Morgan MA. Interactions with industry under the Sunshine Act: an example from gynecologic oncology. *Am J Obstet Gynecol* 2016;214:703–7.
77. Norris P HA, Lexchin J, et al. Drug promotion—what we know, what we have yet to learn—reviews of materials in the WHO/HAI database on drug promotion. *EDM Research Series* 2005.
78. Carroll AE, Vreeman RC, Buddenbaum J, et al. To what extent do educational interventions impact medical trainees' attitudes and behaviors regarding industry-trainee and industry-physician relationships? *Pediatrics* 2007;120:e1528–35.
79. Birkhahn RH, Jauch E, Kramer DA, et al. A review of the federal guidelines that inform and influence relationships between physicians and industry. *Acad Emerg Med* 2009;16:776–81.
80. Sergeant MD HP, Godwin M, Walker DM, et al; *Interactions with the pharmaceutical industry: a survey of family medicine residents in Ontario*. CMAJ: Canadian Medical Association Journal, 1996;155:1243.
81. T Montague B, Fortin VI AH, Rosenbaum J. A systematic review of curricula on relationships between residents and the pharmaceutical industry. *Med Educ* 2008;42:301–8.
82. R. P., Guidelines for faculty involvement in commercially supported continuing medical-education. *Acad Med* 1992.
83. Greenland P. Time for the Medical Profession to Act. *Arch Intern Med* 2009;169:829.